Reviews:

Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667.

Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: New York, **1999**; Vol III, pp. 1177–1235.

Reilly, M.; Oh, T. *Org. Prep. Proceed. Int.* **1994**, *26*, 131–158.

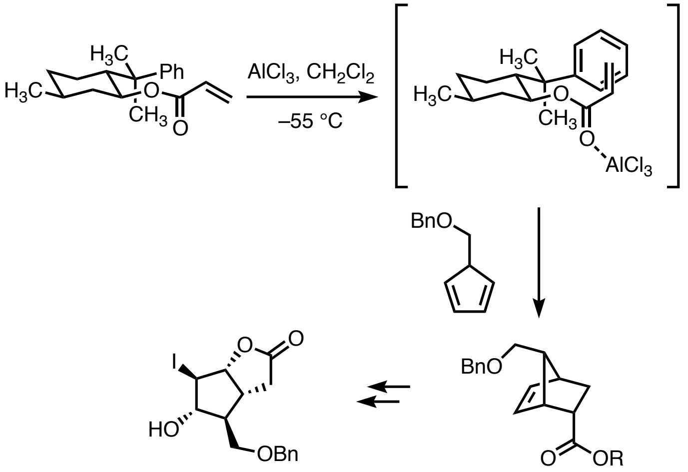
Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007–1019.

Applications in Total Synthesis:

Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698.

Chiral Auxiliaries – Dienophiles:

(–)-8-Phenylmenthol:



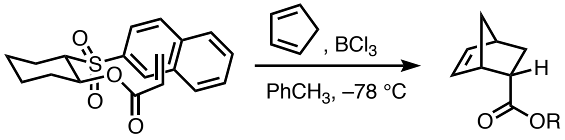
(Intermediate in prostaglandin synthesis)

89%, 97% de

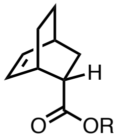
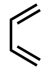
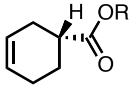
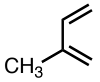
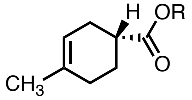
- Endo-selective cycloaddition is proposed to occur from the unblocked β-face of the *s-trans* acrylate-Lewis acid complex.
- A favorable π-stacking interaction is proposed to enhance the stereoselectivity of this process. (Acrylates derived from menthol afford lower diastereoselectivity – ca. 40%).
- (–)-8-phenylmenthol, derived from (–)-pulegone, is commercially available. Recovery of the auxiliary was accomplished in 94% yield following reductive removal.

Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908–6909.
Ensley, H. E.; Parnell, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **1978**, *43*, 1610–1612.

- The stereochemical model for chiral induction by the 8-phenylmenthol controller has been applied in the design of a practical auxiliary for asymmetric Diels–Alder reactions:

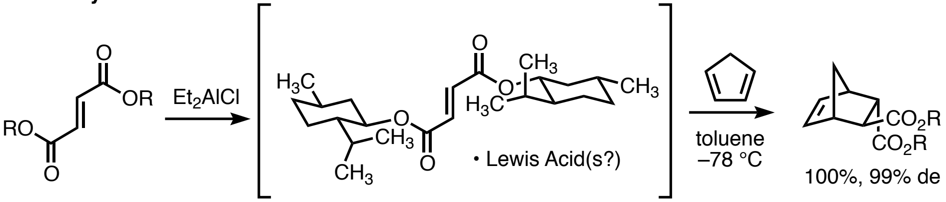


99% yield, 98.5 : 1.5 endo : exo, 97% de

diene	product	yield (%)	endo : exo	de (%)
		94	> 99 : 1	97
		97	--	94
		98	--	94

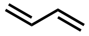
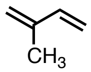
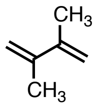
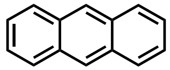
Corey, E. J.; Sarakinos, G. *Org. Lett.* **1999**, *1*, 1741–1744.

Dimenthyl Fumarate:



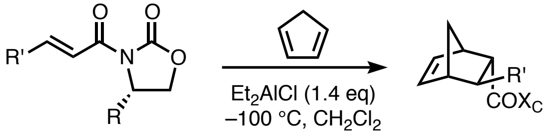
100%, 99% de

- The menthyl auxiliaries exhibit cooperative asymmetric induction in the case of the fumarate ester, resulting in excellent selectivity for cycloaddition from the back face.

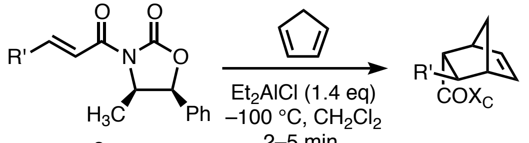
Diene	Lewis Acid	Temperature (°C)	Yield	de (%)
	*i*-Bu_2AlCl	–40	56	95
	*i*-Bu_2AlCl	–20	94	95
	Et_2AlCl	–20	70	96
	$AlCl_3$	25	92	99

From: Furuta, K.; Iwanaga, K. Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4507–4510. Kent Barbay

N-Acyloxazolidinone Dienophiles:



1 R = CH(CH$_3$)$_2$
2 R = CH$_2$Ph

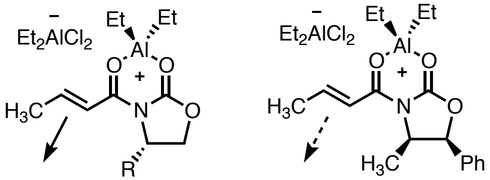


3

dienophile	endo : exo	endo dr	isolated yield	isolated dr
1, R' = H	>100 : 1	93 : 7	81	>99 : 1
2, R' = H	>100 : 1	95 : 5	78	97 : 3
3, R' = H	100 : 1	5 : 95	82	<1 : 99
1, R' = CH$_3$	48 : 1	95 : 5	82	>99 : 1
2, R' = CH$_3$	55 : 1	97 : 3	83	99 : 1
3, R' = CH$_3$	60 : 1	2 : 98	88	<1 : 99
1, R' = Ph[a]	b	93 : 7	83	>99 : 1

a. Reaction run at –20 °C, 2.5 h.
b. Exo product not observed by 500 MHz ^{1}H-NMR.

- The high reactivity of the unsaturated carboximides is highlighted by tolerance of β-substitution on the dienophile, which is not typically the case for chiral ester dienophiles.
- The stereochemical results are consistent with the following models:



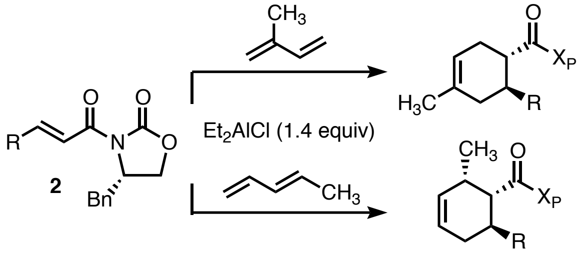
- cycloaddition occurs from the less sterically encumbered face
- the reactive dienophile is a chelated cationic species
- the *s-cis* conformation of chelated acyl oxazolidinones is assumed to be favored

- (Z)-unsaturated imides and β,β-disubstituted imides have limited applicability due to competing isomerization or low reactivity.

Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261–4263.

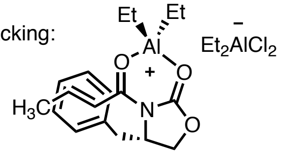
Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.

- Diene scope: includes dienes less reactive than cyclopentadiene (e.g. acyclic dienes). In this case, imide **2** afforded uniformly higher diastereoselectivities than **1** or **3**.



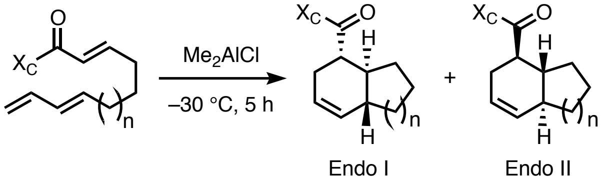
R	diene	dr	isolated yield (%)	isolated dr
H	isoprene	95 : 5	85	> 99 : 1
H	piperylene	>100 : 1	84	> 99 : 1
CH$_3$	isoprene	94 : 6	83	> 99 : 1
CH$_3$	piperylene	95 : 1 : 2 : 2	77	> 99 : 1

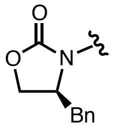
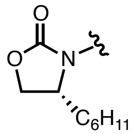
- The enhanced stereoselectivity of dienophile **2** is attributed to π-stacking:



Evans, D. A.; Chapman, K. T.; Hung, D. T.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184–1186.

- The oxazolidinone auxiliaries have been applied to asymmetric intramolecular Diels–Alder reactions:



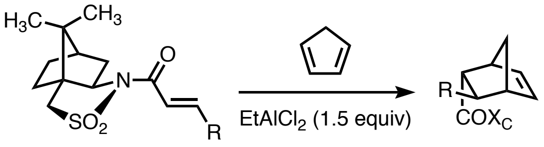
X$_C$	n	dr (Endo I : Endo II)	Isolated yield (%)[a]
	1 2	95 : 5 97 : 3	73 88
	1 2	3 : 97 6 : 94	65 70

a. Refers to purified products, de >99%.

Evans, D. A.; Chapman, K. T.; Bisaha, J. *Tetrahedron Lett.* **1984**, 25, 4071–4074.

Kent Barbay

Camphor-derived *N*-Enoyl Sultams:

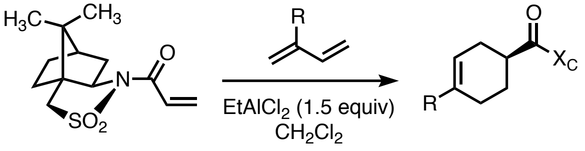


R	Temperature (°C)	Time (h)	endo : exo	endo dr	yield
H	–130	6	99.5 : 0.5	97.5 : 2.5	83[a]
CH_3	–78	18	96 : 4	99 : 1	91[b]

a. Recrystallized yield, de ≥ 99%.

b. Crude yield of material with indicated isomeric purity.

- Acyclic dienes are suitable substrates in the case of (unsubstituted) *N*-acryloyl sultams:



R	Temperature (°C)	Time (h)	dr	yield[a]
H	–78	6	98.5 : 1.5	81
CH_3	–94	6	97 : 3	64

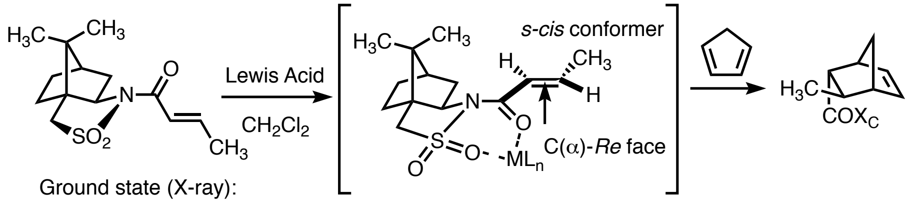
a. Recrystallized yield, de ≥ 99%.

- Both antipodes of the chiral auxiliary are available; they are synthesized in two synthetic steps from camphor-10-sulfonyl chloride.
- Recovery of the auxiliary is possible after reductive or hydrolytic removal.
- The cycloadducts tend to be crystalline solids, facilitating purification.

Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chem. Acta.* **1984**, *67*, 1397–1401.

Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B.M. and Fleming, I. Eds.; Pergamon: Oxford, 1991, Vol. 5, pp. 315–399.

- The stereochemical outcome is rationalized by the following model, involving a chelated complex:



Ground state (X-ray):
C=O/C=C *s-cis*,
NSO_2/C=O *s-trans*

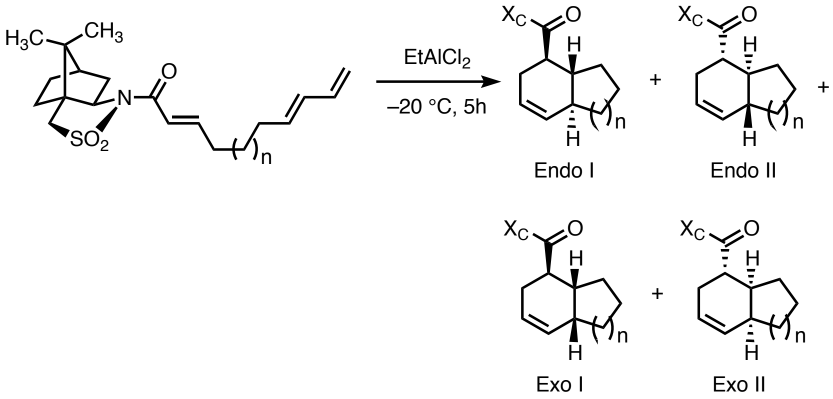
$TiCl_4$ Complex (X-ray)

Oppolzer, W.; Rodriquez, I.; Blagg, J.; Bernardinelli, G. *Helv. Chem. Acta.* **1989**, *72*, 123–131.

- α,β-unsaturated amides display a general preference for the *s-cis* conformer.

Montaudo, G.; Librando, V.; Caccamese, S.; Maravigna, P. *J. Am. Chem. Soc.* **1973**, *95*, 6365–6370.

- The camphor-derived sultam auxiliary has also been applied to intramolecular reactions:



n	dr (Endo I : Endo II : [Exo I + Exo II])	Isolated yield (%)[a]
1	>97.4 : 2.5 : <0.1	75
2	94.0 : 2.6 : 3.4	53

a. Refers to crystallized Endo I, de >99%.

Oppolzer, W.; Dupuis, D. *Tetrahedron Lett.* **1985**, *26*, 5437–5440.

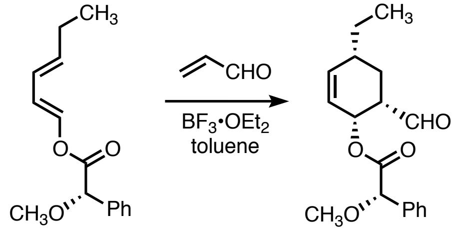
Kent Barbay

Chiral Auxiliaries – Dienes:

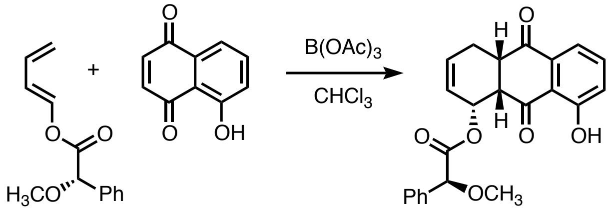
Review: Barluenga, J.; Suárez-Sobrino, A.; López, L. A. *Aldrichimica Acta.* **1999**, *32*, 4–15.

Chiral 1-heterosubstituted dienes:

- 1-*O*-methylmandeloxy substituted dienes (Trost's dienes):



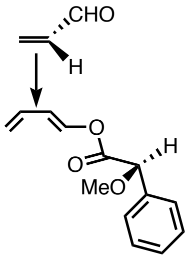
endo only
60% de, 92% yield



endo only
> 97% de, 98% yield

Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595–7596.

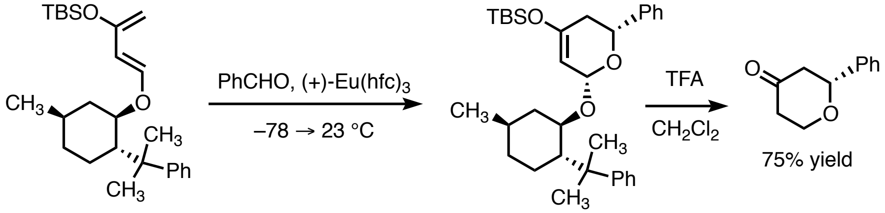
- A stereochemical model rationalizing these results has been presented by Thornton:



- a transition state conformation in which the phenyl substituent is perpendicular to the plane of the diene is proposed, favoring approach from the top face.

Siegel, C.; Thornton, E. R. *Tetrahedron Lett.* **1988**, *29*, 5225–5228.
Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 7630–7640.

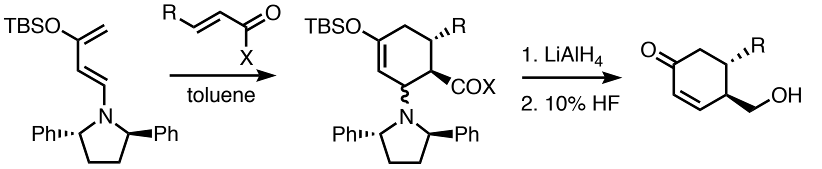
- 1-Alkoxy-3-silyloxy-1,3-butadienes (auxiliary-modified analogs of Danishefsky's diene):

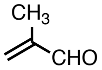
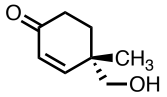
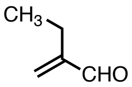
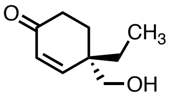
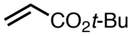
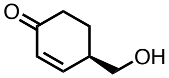
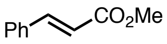
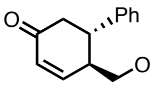
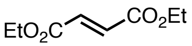
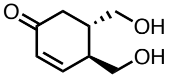
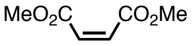
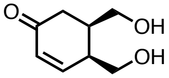


92% de

Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060–7067.

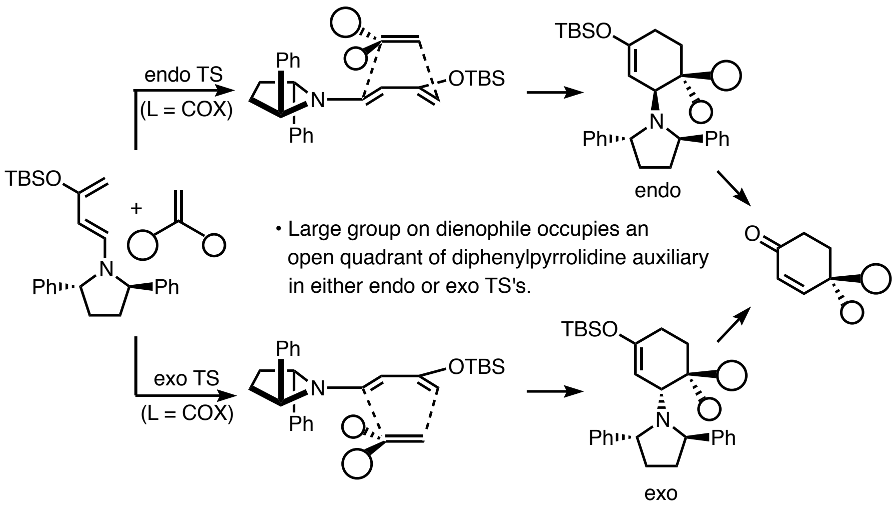
- 1-amino-3-silyloxy dienes:



dienophile	product	yield (%)	ee(%)
		79	88
		87	88
		86	98
		66	96
		82	92
		64	98

Kent Barbay

- Stereochemical Model:



- Large group on dienophile occupies an open quadrant of diphenylpyrrolidine auxiliary in either endo or exo TS's.

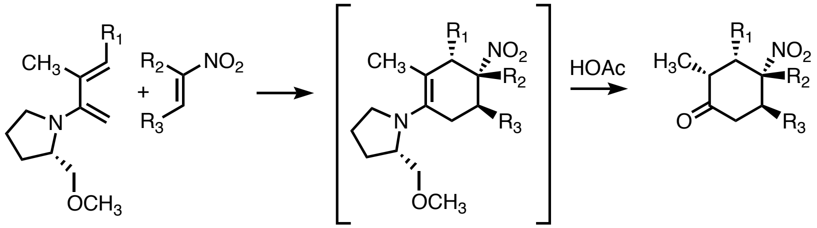
- Both endo and exo cycloadducts are transformed to the same enantiomer of the cyclohexenone product, allowing the use of dienophiles that do not undergo cycloaddition with high endo/exo selectivity.

Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562–9573.

Chiral 2-heterosubstituted dienes:

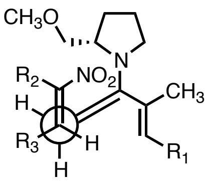
- 2-amino dienes:

Review: Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023–1035.



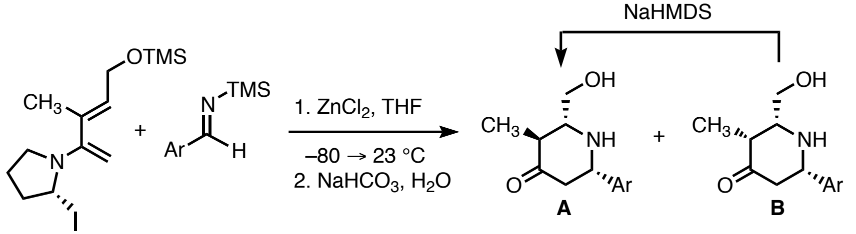
R_1	R_2	R_3	yield (%)	ee (%)
H	H	Ph	48	98
CH_2OTBS	H	Ph	63	94
CH_2OTBS	H	Me	48	95
CH_2OTBS	H	*i*-Pr	56	92
CH_2OTBS	-$(CH_2)_4$-		70	94

- These cycloadditions are proposed to proceed by a stepwise mechanism:



- Alkyl substitution at C_3 of the diene appears to be required, probably to restrict the conformation of the prolinol group as shown.

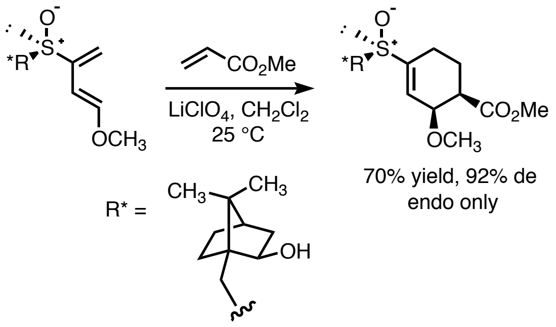
Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1997**, *62*, 6746–6753.
Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242–1244.



Ar	combined yield (%)	ee (%) (pdt **A**)
3-furyl	51	> 98
4-MeOPh	43	90
Ph	65	95

Barluenga, J.; Anzar, F.; Ribas, C.; Valdés, C.; Fernández, M.; Cabal, M.-P.; Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805–811.

- Sulfinyl-substituted dienes:



70% yield, 92% de
endo only

Aversa, M. C.; Barattuci, A.; Bonaccorsi, P.; Giannetto, P.; Jones, D. N. *J. Org. Chem.* **1997**, *62*, 4376–4384.

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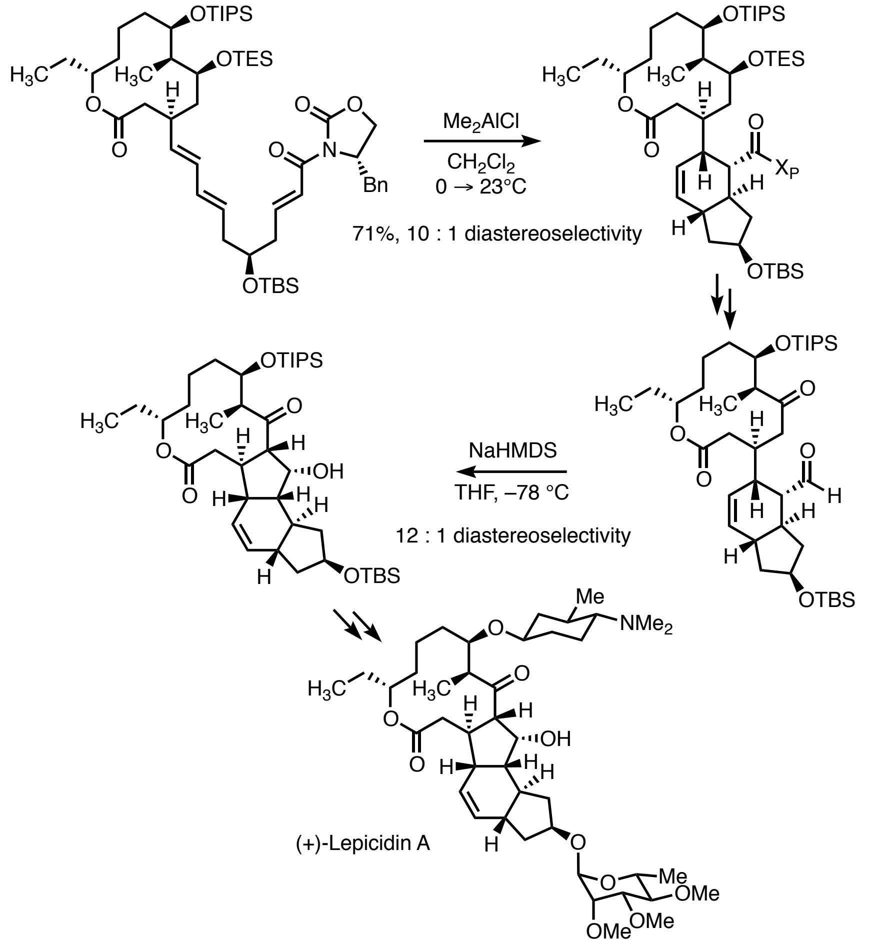
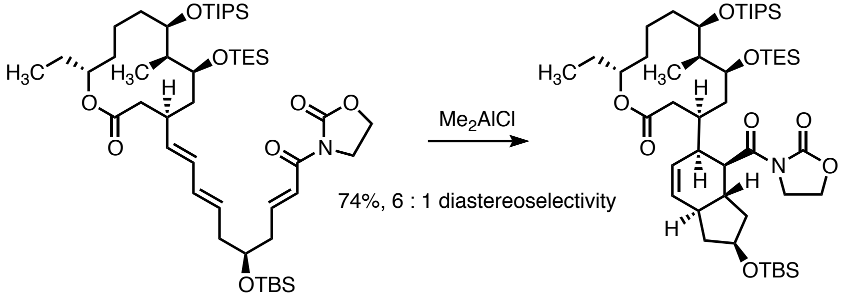
Chiral Auxiliaries for Asymmetric Diels-Alder Reations – Applications in Synthesis:

(+)-Lepicidin A:

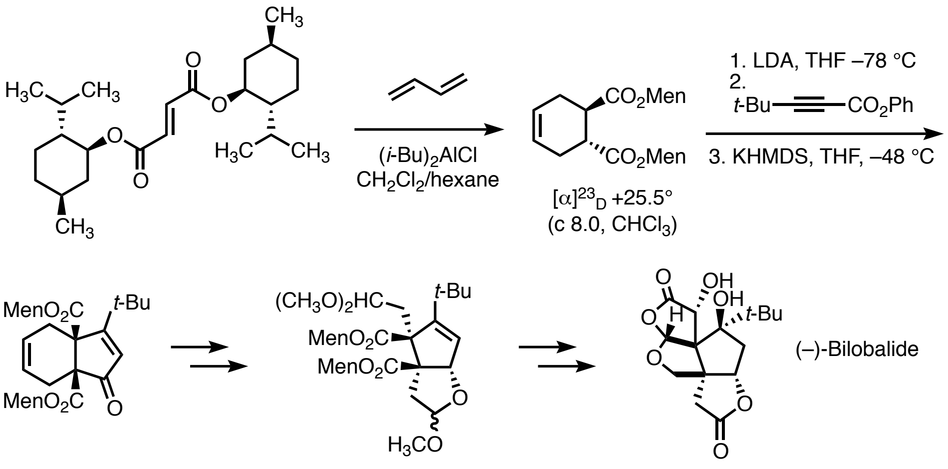


- A control experiment showed the auxiliary overcame inherent stereochemical bias in the substrate:



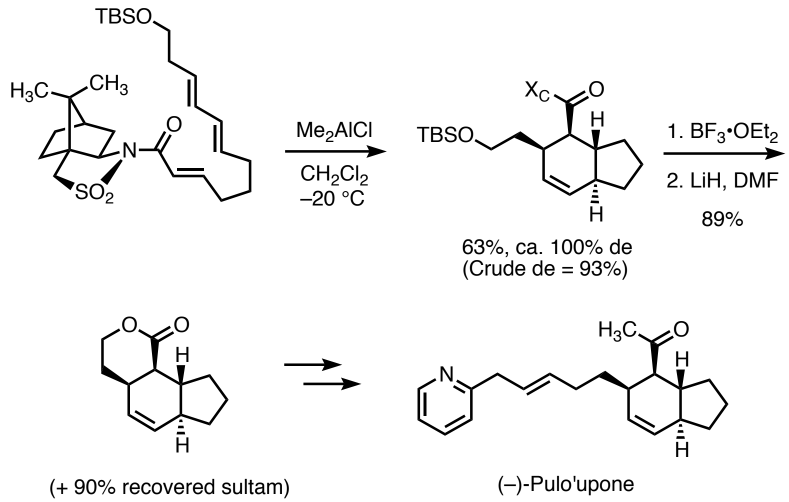
Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513.

(–)-Bilobalide:



Corey, E. J.; Su, W.-G. *Tetrahedron Lett.* **1988**, *29*, 3423–3426.

Pulo'upone:



Oppolzer, W.; Dupuis, D.; Poli, G.; Raynham, T. R.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, 29, 5885–5888.

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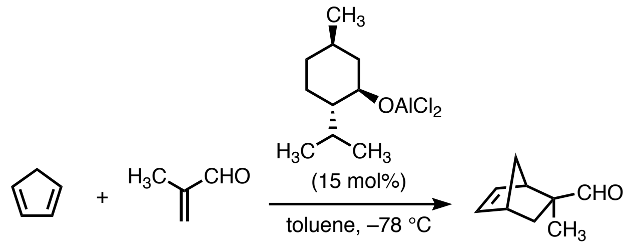
Catalytic, Asymmetric Diels–Alder Reactions:

- The first reported catalytic, asymmetric Diels–Alder reaction:

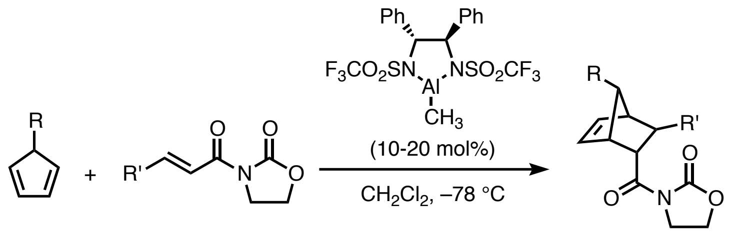


69%, 72% ee
exo : endo = 98 : 2

- The exo selectivity of α-substituted acroleins is general.

Hasimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437–438.

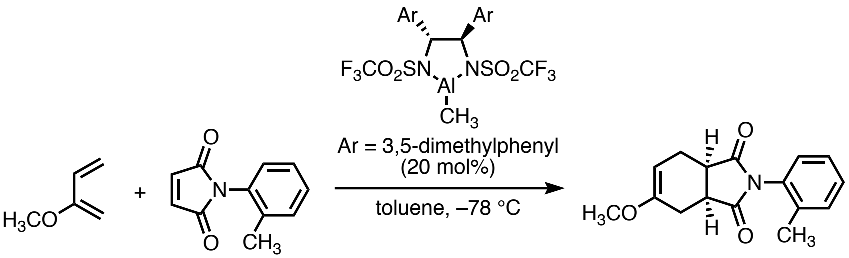
C_2-symmetric Diazaaluminolidine Catalysts:



R	R'	endo : exo	ee (%)	yield (%)
H	H	>50 : 1	91	92
H	CH_3	96 : 4	94	88
CH_2OBn	H	–	95	94

Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. *J. Am. Chem. Soc.* **1989**, *111*, 5493–5495.

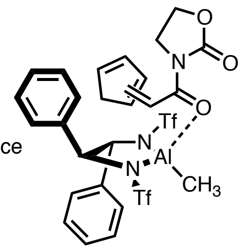
- A modified catalyst expanded the scope of this system to include maleimide dienophiles:



98%, 93% ee

Corey, E. J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* **1994**, *116*, 12089–12090.

- Both antipodes of the 1,2-diaryl-1,2-diaminoethane ligands are available, via resolution employing tartaric acid: Corey, E. J.; Lee, D.-H.; Sarshar, S. *Tetrahedron: Asymmetry* **1995**, *6*, 3–6.
- Proposed transition-state assembly:

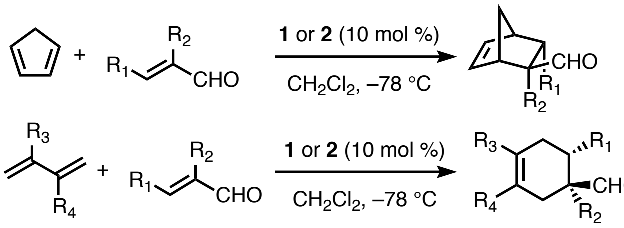


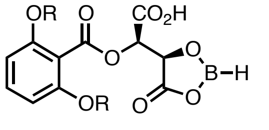
- Phenyl blocks front face
- Non-chelated binding mode
- *s-trans* dienophile conformer

- This model is supported by ^1H, ^{13}C, and ^1H NOE data for the 1 : 1 dienophile : catalyst complex, as well as X-ray diffraction analysis of the catalyst dimer.

Corey, E. J.; Sarshar, S. *J. Am. Chem. Soc.* **1992**, *114*, 7938–7939.

Chiral (Acyloxy)borane (CAB):





1 R = Me
2 R = *i*-Pr

catalyst	R_1	R_2	R_3	R_4	endo : exo	ee (%)	yield (%)
1	H	H	–	–	88 : 12	84	90
1	H	H	CH_3	CH_3	–	84	53
1	H	CH_3	–	–	11 : 89	96	85
1	H	CH_3	CH_3	CH_3	–	97	61
1	H	CH_3	CH_3	H	–	91	65
1	CH_3	CH_3	–	–	3 : 97	90	91
2	H	Br	–	–	6 : 94	95	100
2	H	Br	CH_3	CH_3	–	95	80
2	CH_3	Br	–	–	>99 : 1	98	100

- α-substituted α,β-unsaturated aldehyde dienophiles give optimal selectivities.
- Both enantiomers of the CAB catalyst are available, from (+) and (–)-tartaric acid.

Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1483–1484.
Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 6917–6919.

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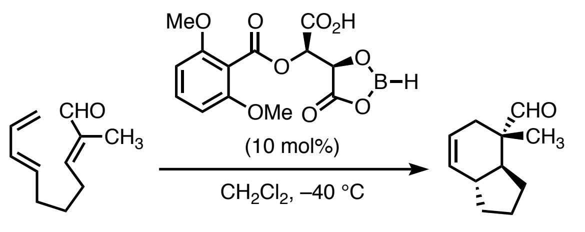
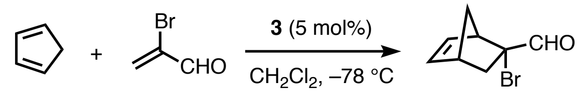
- Yamamoto's CAB catalyst has been applied to intramolecular reactions:



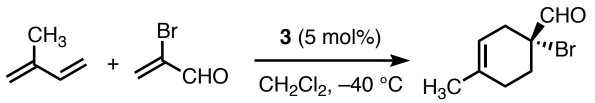
84%, 92% ee
99 : 1 endo : exo

Furuta, K.; Kanematsu, A.; Yamamoto, H.; Takaoka, S. *Tetrahedron Lett.* **1989**, *30*, 7231–7232.

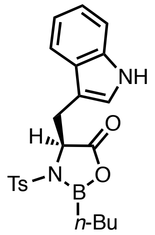
Oxazaborolidine Catalysts:



95%, 99% ee
96 : 4 exo : endo



76%, 92% ee

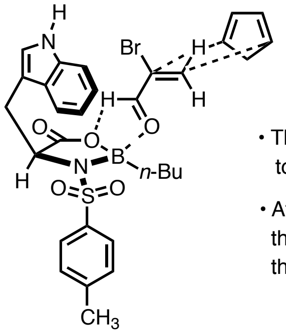


3

- α-substitution on the aldehyde component is required for high enantioselectivity.
- The tryptophan-derived ligand was efficiently recovered.

Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966–8967.

- Physical and chemical studies of this system led to the following transition-state model:



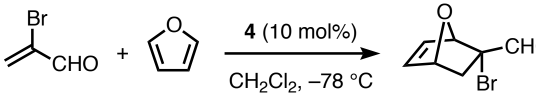
- The complex of the *s-cis* conformer is proposed to be the reactive species.
- Attractive π-stacking interactions between the indole and the dienophile organize the TS, and result in reaction from the unblocked (back) face.

Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290–8292.

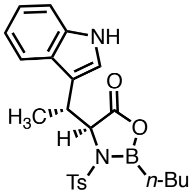
- Lewis acids complex aldehydes *syn* with respect to the formyl proton – for a review on the conformations of carbonyl-Lewis acid complexes, see: Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256–272.

- Formyl CH--O hydrogen bonding is proposed as an additional organizational element leading to the excellent enantioselectivities observed. For the application of the formyl CH--O hydrogen bond postulate to the understanding of enantioselective reactions involving chiral boron Lewis acids and aldehydes, see: Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, *38*, 37–40.

- A modified oxazaborolidine catalyzes cycloadditions to furan:



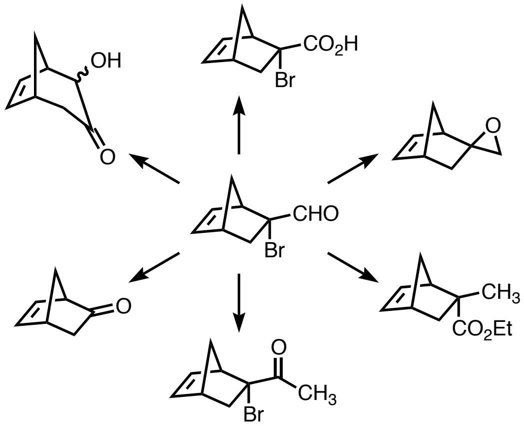
>98%, 92% ee



4

Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979–3982.

- Corey has demonstrated the synthetic versatility of the 2-bromoacrolein/cyclopentadiene cycloaddition adducts:



Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966–8967.

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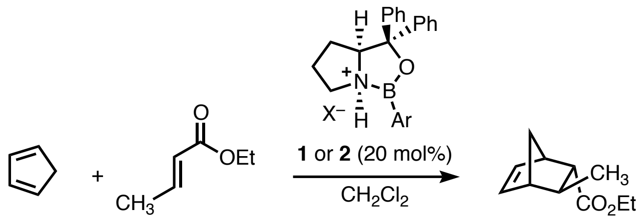
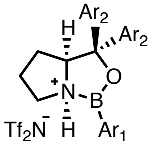
Cationic Oxazaborolidine Catalysts:



Ar = *o*-tolyl

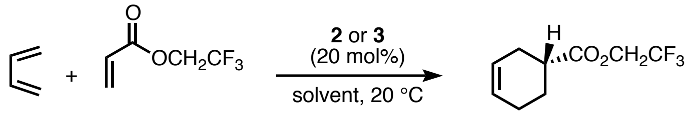
catalyst	X	temp (°C)	time (h)	yield (%)	endo:exo	ee (%, endo)
1	OTf	4	72	46	91:9	>98
2	NTf_2	20	16	94	89:11	97

- The neutral oxazaborolidine catalyst does not exhibit catalytic activity in the Diels–Alder reaction of cyclopentadiene with methacrolein.
- Early experiments were conducted with catalyst **1**; it was subsequently shown that the triflimide-activated catalyst **2** exhibits greater thermal stability and higher catalytic activity.
- When using less reative dienes, the related 3,5-dimethylphenyl catalyst **3** is often superior to **2**.



Ar_1 = *o*-tolyl
Ar_2 = 3,5-dimethylphenyl

3

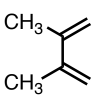
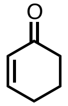
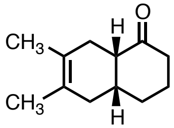
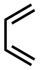
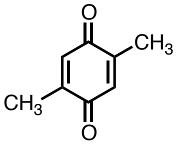
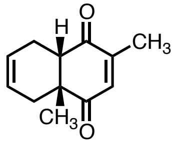
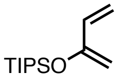
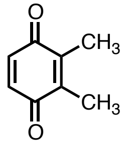
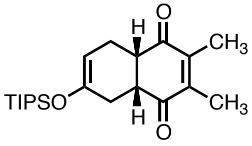
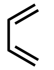
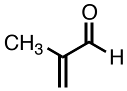
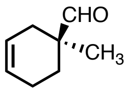
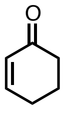
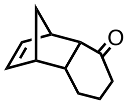


catalyst	solvent	time (h)	yield (%)	ee (%)
2	toluene	40	78	88
3	neat	24	96	95

Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808.
Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992.
Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388.

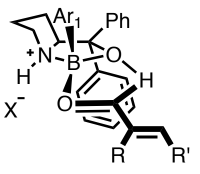
- A useful set of predictive selection rules has been developed for the oxazaborolidinium-mediated Diels–Alder reaction of substituted quinones:
  Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800.

- Catalysts **1**, **2**, and **3** exhibit broad substrate scope and predictable selectivities. Enantioselectivities are typically >90%; *endo:exo* ratios are uniformally high (4:1→>99:1).

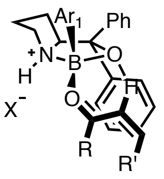
catalyst[a]	diene	dienophile	product	time (h), temp (°C)	yield, ee (%)
2 **3**				16, 20 24, 4	99, 64 99, 77
2				48, –78	97, 91
2				2, –95	98, >99
1				24, –78	85, 94
1				16, –20	97, 93[b]

[a] 20 mol% catalyst. [b]*endo:exo* = 91:9.

- Corey has proposed the following pre-transition-state complexes:



enals

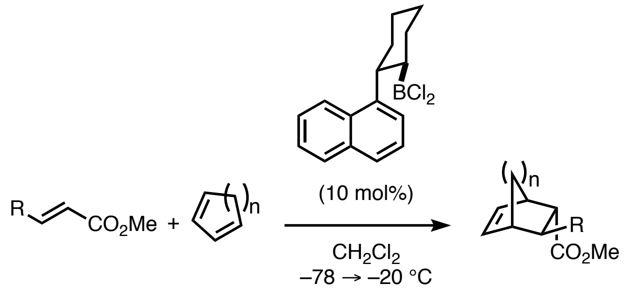


quinones, enones, and α,β-unsaturated esters

- The phenyl [or 3,5-dimethylphenyl in the case of **3** (not shown)] substituent is proposed to engage in π-stacking with the dienophile.
- The diene approaches the catalyst–dienophile complex from the face opposite the phenyl group.
- The existence of an O—HC interaction is supported by studies of enal-, and enone-BF_3 complexes.
- Note the sense of stereoinduction for enals is opposite that of quinones, enones, and α,β-unsaturated esters.

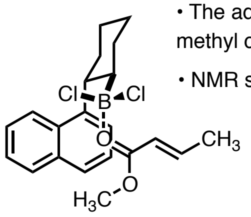
Seth B. Herzon

Alkyldichloroboranes:



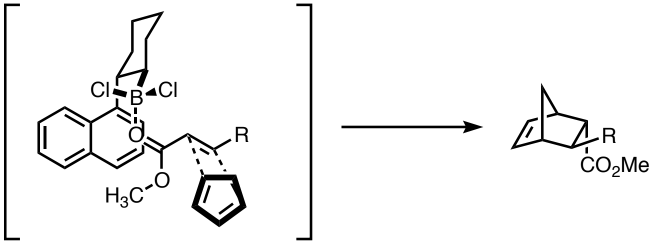
R	n	ee (%)	yield (%)
H	1	97	97
CH_3	1	93	91
CO_2Me	1	90	92
H	2	86	83

- The catalyst was prepared by resolution with (–)-menthone.



- The adjacent figure illustrates the approximate conformation of the catalyst• methyl crotonate complex (X-ray).
- NMR studies suggest this conformation is retained in solution.
  - The *s-trans* crotonate conformer is observed.
  - The carbonyl is positioned over and parallel to the naphthylene, within van der Waals contact (3.2 Å) (π-stacking interaction).
  - Complexation of Lewis acids *anti* to ester C–O bonds appears to be a general phenomenon.

- The absolute stereochemical configuration of the products is consistent with a transition-state model closely related to the observed ground state complex:

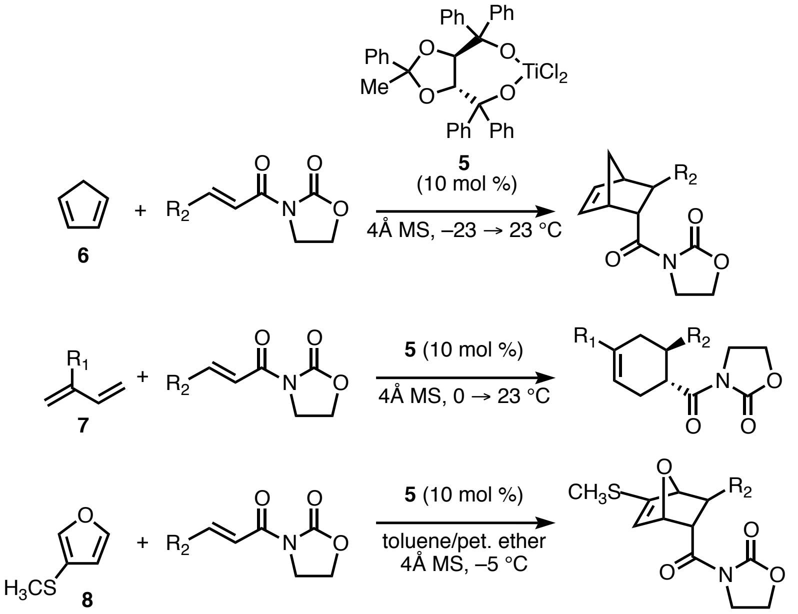


- The naphthalene substituent forces the dienophile to approach from the front face.

Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794–7795.

Titanium-TADDOL:

- Narasaka's Ti complex catalyzes a wide variety of Diels–Alder reactions with high selectivities:



Diene	R_1	R_2	endo : exo	ee (%)	yield (%)	reference
6	–	H	n.d.	88	81	2
6	–	CH_3	87 : 13	94	91	1
6	–	Ph	92 : 8	80	76	1
7	H	H	–	93	81	2
7	H	CO_2Me	–	91	84	1
7	CH_3	H	–	>96	93	2
7	CH_3	CO_2Me	–	94	94	1
8	–	H	85 :15	87	97	3
8	–	CO_2Me	78 : 22	86	99	3

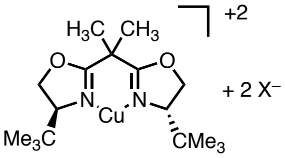
1. Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340–5345.
2. Narasaka, K.; Tanaka, H.; Kanai, F. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 387–391.
3. Narasaka, K.; Yamamoto, I. *Chem. Lett.* **1995**, 1129–1130.

- A number of transition-state models have been proposed; the analysis is complicated by the number of coordination possibilities available in octahedral complexes.

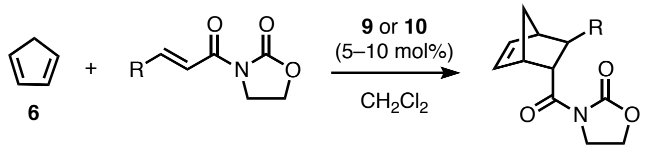
Kent Barbay

Bis(oxazoline) Copper Complexes:

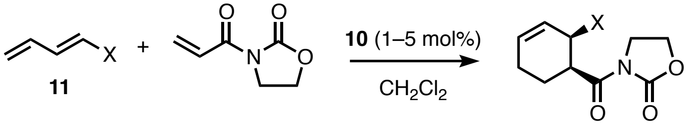
- Evans' copper (II) catalysts have been successfully applied to a wide array of cycloaddition substrates:



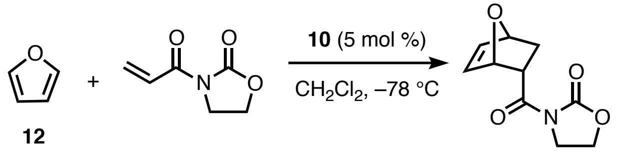
9 X = OTf
10 X = SbF_6



6



11



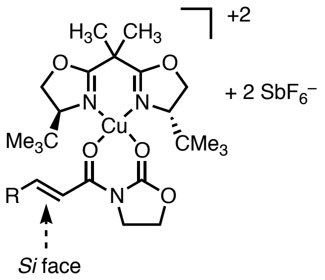
12

Catalyst	Diene	X	R	endo : exo	ee (%)	yield (%)
9	**6**	–	H	98 : 2	>98	86
9	**6**	–	CO_2Et	94 : 6	95	92
9	**6**	–	CH_3	96 : 4	97	85
10	**6**	–	Ph	91 : 9	96	96
10	**6**	–	Cl	86 : 14	95	96
10	**11**	OAc	–	85 : 15	96	75
10	**11**	SPh	–	98 : 2	98	84
10	**11**	NHCbz	–	72 : 28	90	54
10	**12**	–	–	80 : 20	97	97

- Catalyst **10** (X = SbF_6) uniformly provides higher reactivity and higher levels of asymmetric induction than **9** (X = OTf), which was reported earlier.

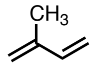
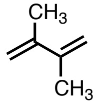
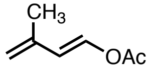
Evans. D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798–800.

- The stereochemical results are in all cases consistent with the following model:



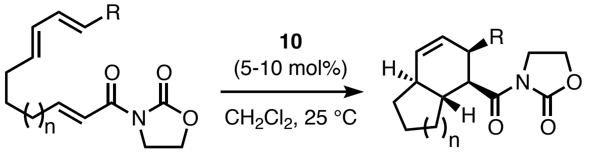
- Square planar geometry about Cu
- Imide binds in a bidentate fashion
- *s-cis* dienophile configuration
- diene approaches from the back face; the front face is blocked by the *t*-Bu group

- Acyclic dienes unsubstituted at the 1-position afforded lower enantioselectivities:

Catalyst	Diene	endo : exo	ee (%)	yield (%)
10		–	59	81
10		–	65	78
10		27 : 73	98	57[a]

a. Isolated yield of enantiomerically and diastereomerically pure material.

- These dienes (substituted at C3) are proposed to approach via an exo transition state. The exo transition state is apparently only selective in the case of 1-substituted dienes.
- Calalyst **10** is also effective for intramolecular Diels–Alder reactions:

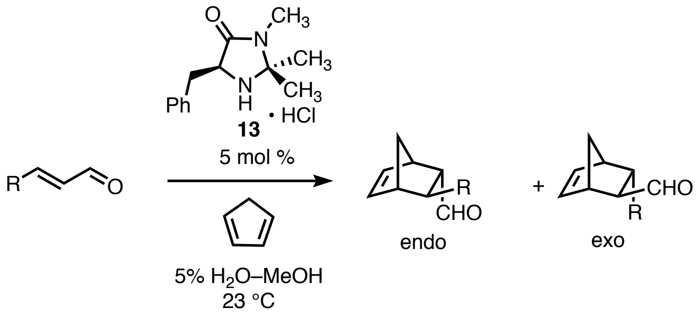


R	n	endo : exo	ee (%)	yield (%)
H	1	>99 : 1	86	89
Ph	1	>95 : 5	92	86
Ph	2	84 : 16	97	97

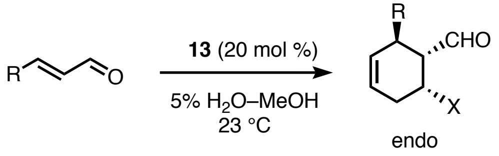
Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460–6461.
Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559–7573.
Evans, D. A.; Barnes, D. M.; Johnson, J.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594.

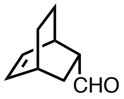
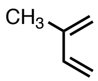
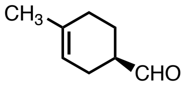
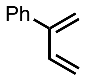
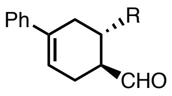
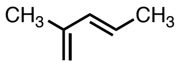
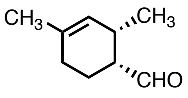
Kent Barbay

Asymmetric Catalysis of the Diels–Alder Reaction with a Chiral Amine through Reversible Iminium Ion Formation:

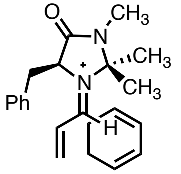


R	yield	exo : endo	exo ee (%)	endo ee (%)
Me	75	1 : 1	86	90
n-Pr	92	1 : 1	86	90
i-Pr	81	1 : 1	84	93
Ph	99	1.3 : 1	93	93
Furyl	89	1 : 1	91	93



diene	R	product	yield	endo : exo	ee (%)
	H		82	14 : 1	94
	H		84	–	89
	H		90	–	83
	CH_3		75	–	90
	H		75	5 : 1	90

- Stereochemical model:

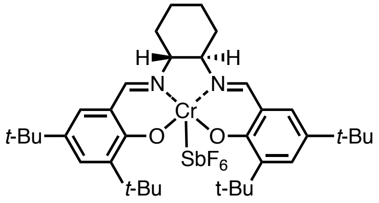


- Selective formation of the (illustrated) (*E*)-iminium isomer is proposed, avoiding unfavorable interactions between the substrate olefin and the geminal dimethyl substituents.
- The benzyl substituent shields the β-face of the dienophile.

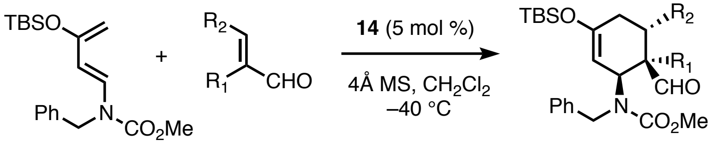
Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

Jacobsen's Catalyst:

- Jacobsen's Cr (III) salen complex **14** catalyzes highly enantioselective Diels–Alder reactions of 1-amino-3-silyloxydienes and acroleins:



14



R_1	R_2	yield	ee (%)
Me	H	93	97
Et	H	91	97
i-Pr	H	92	>97
$TBSO(CH_2)_2$	H	93	95
TBSO	H	86	>97
$–(CH_2)_3–$		76	96

- No exo products were observed in these cycloadditions.

Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 7843–7844.

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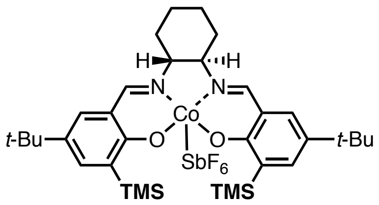
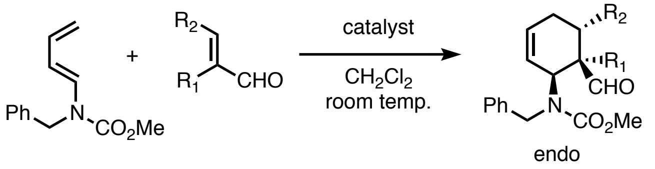
- X-ray analysis of the (1*R*, 2*R*)-salen–Co(III)-SbF_6•2PhCHO complex suggested that replacing the *t*-butyl groups with bulkier trimethylsilyl substituents might create a steric interaction (between the trimethylsilyl groups) that would twist the aromatic rings out of plane.

- This modification has resulted in an exceptionally selective and active Diels–Alder catalyst:





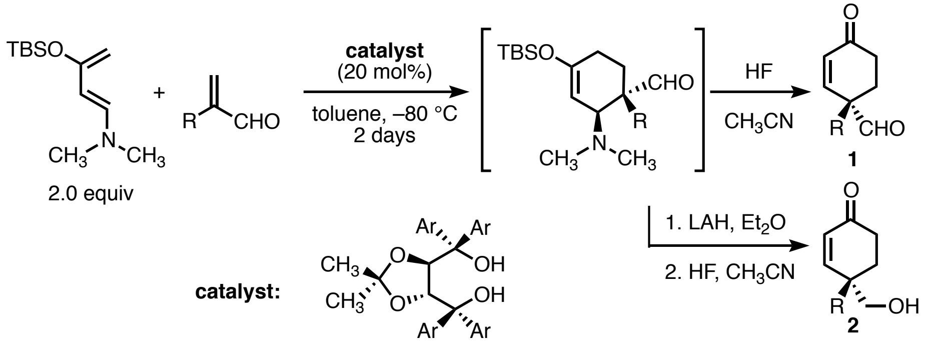
entry	R_1	R_2	mol % cat.	time (h)	yield	ee (%)
1	CH_3	H	4	1	98	98
2	CH_3	H	0.05	72	93	98
3	CH_2CH_3	H	0.1	30	93	>97
4	$TBSO(CH_2)_2$	H	0.5	18	100	>97
5[a]	H	H	0.1	18	100	85
6[b]	H	H	2	40	90	>97
7	$–(CH_2)_4–$		2	72	78	>95

[a] Reaction performed at 0 °C. [b] Reaction performed at –78 °C.

- Entry 2 represents the lowest substrate/catalyst ratio (s:c = 2000) reported for an asymmetric Diels–Alder reaction.

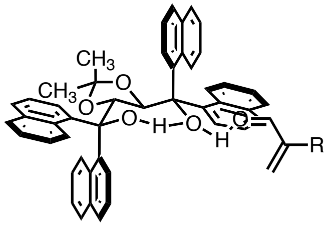
Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 5950.

Catalysis via Hydrogen Bonding



entry	R	% yield **1**	% yield **2**	% ee of **2**
1	H	—	77	73
2	CH_3	85	82	91
3	CH_2CH_3	80	83	88
4	*i*-Pr	77	81	92
5	Bn	84	82	89
6	CH_2CH_2OTBS	80	80	86

- The following stereochemical model has been proposed:

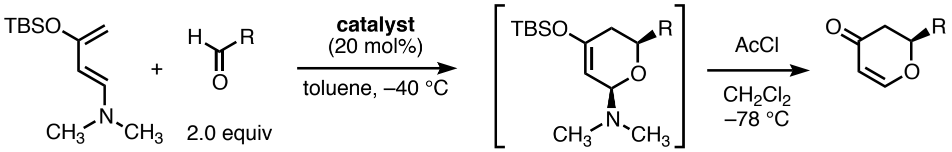


- The diene approaches from the face opposite the napthyl group.

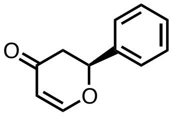
Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846.

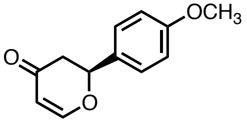
Catalytic, Asymmetric Hetero-Diels–Alder Reactions:

The same TADDOL derivative catalyzes hetero-Diels–Alder reactions:

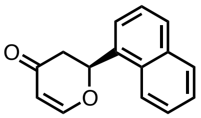


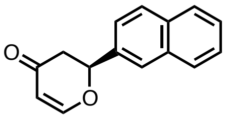
- Products:

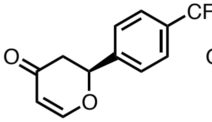

70%, >98% ee



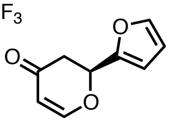
68%, 94% ee

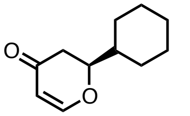

69%, >98% ee

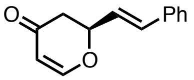

97%, 94% ee



68%, 94% ee


67%, 92% ee


64%, 86% ee



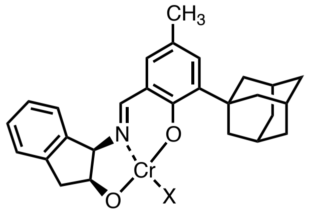
52%, >94% ee

Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature*, **2003**, *424*, 146.

- A 2nd-generation catalyst was developed, expanding the substrate scope. See: Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.

Seth B. Herzon

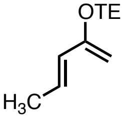
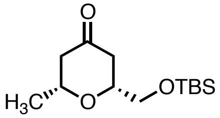
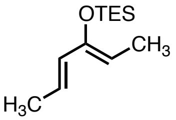
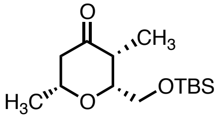
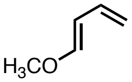
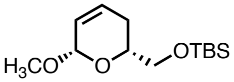
R	ee (%)	yield (%)
Ph	90	72
CH_2OTBS	>99	97
CH_2OBn	94	94
n-C_5H_{11}	98	85
$(CH_2)_4CH{=}CH_2$	98	78
CH_2CH_2Ph	98	78
2-furyl	95	77



14 X = SbF_6
15 X = Cl

- The diastereoselectivity was >95% in all cases, favoring the illustrated endo product.
- Use of acetone as solvent in the cycloaddition generally improves enantioselectivities, and is critical in the case of aromatic aldehydes.
- Both enantiomers of the aminoindanol ligand are commercially available.

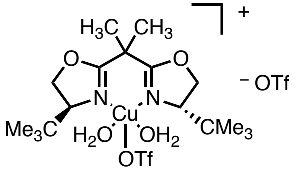
- Excellent enantioselectivities were maintained with several other dienes in reactions catalyzed by **15**:

Diene	Product	ee (%)	yield (%)
		98	78
		91	50
		>99	91

- This is the first effective method for the asymmetric HDA reaction between dienes with less than two oxygen substituents and unactivated carbonyl compounds.

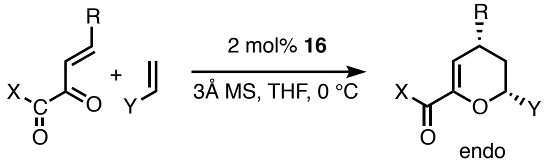
Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2398–2400.

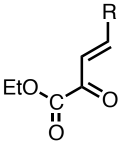
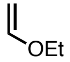
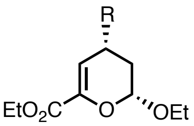
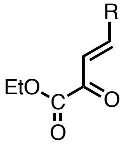
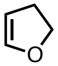
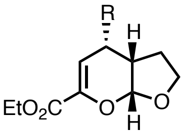
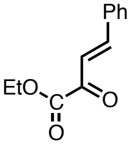
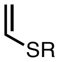
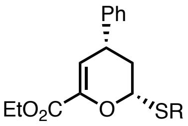
Inverse Electron Demand Hetero-Diels–Alder Reactions catalyzed by Bis(oxazoline) Copper(II) Complexes:



16

- air-stable, solid catalyst



hetero diene	hetero dienophile	product	endo : exo	yield (%)	ee (%)
					
		R = Me	24 : 1	87	97
		R = Ph	> 20 : 1	93	97
		R = *i*-Pr	22 : 1	95	96
		R = OMe	59 : 1	90	98
					
		R = Ph	16 : 1	96	97
		R = *i*-Pr	16 : 1	94	95
					
		R = Et	> 20 : 1	94	97
		R = Ph	> 20 : 1	91	99

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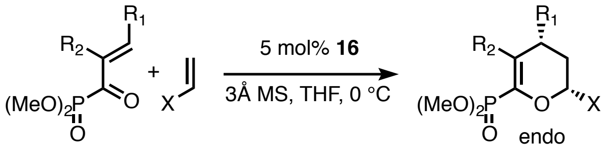
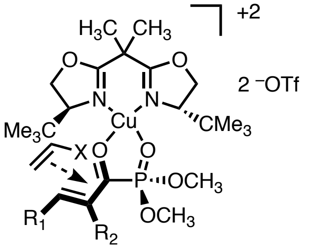


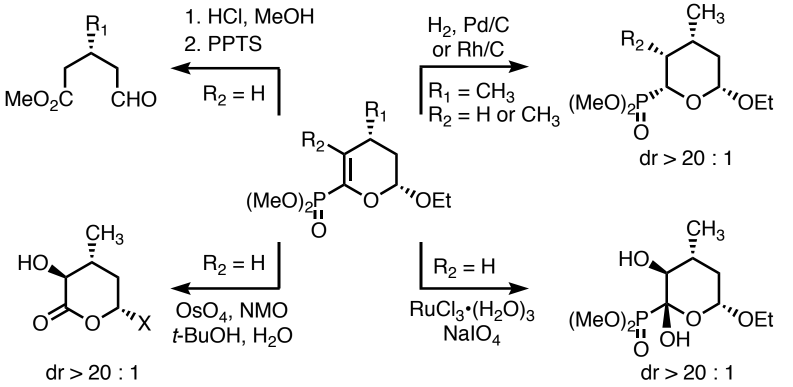
R_1	R_2	X	yield (%)	endo : exo	ee (%)
Me	H	OEt	84	36 : 1	93
Ph	H	OEt	95	22 : 1	97
i-Pr	H	OEt	92	22 : 1	95
OEt	H	OEt	92	44 : 1	97
Me	Me	OEt	98	25 : 1	≥90
Me	H	SEt	75	16 : 1	96

- The hetero-Diels–Alder reactions catalyzed by **16** have a favorable temperature-enantioselectivity profile, affording dihydropyrans with high enantioselectivities even at 0 °C.
- Stereochemical Model:



- square planar transition structure
- heterodiene binds in a chelated fashion
- attack of heterodienophile occurs from the less hindered α-face

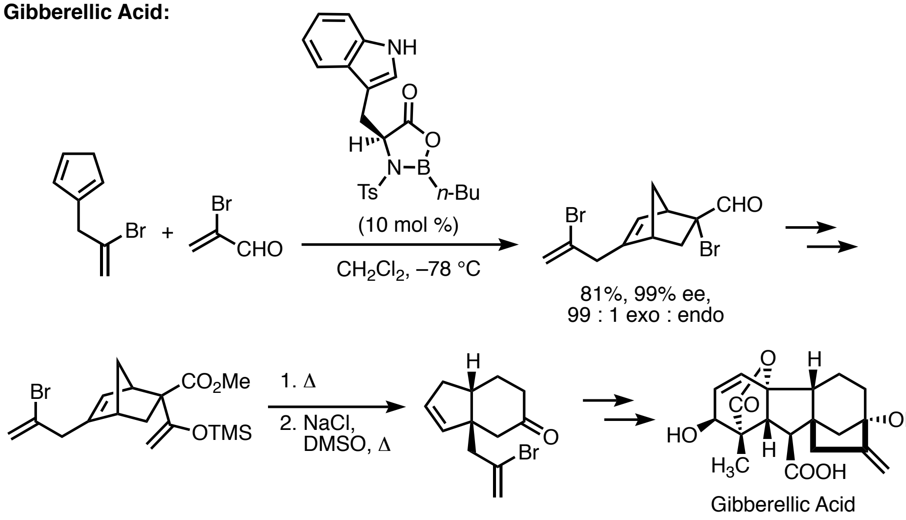
- The product dihydropyrans are synthetically versatile:



Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.

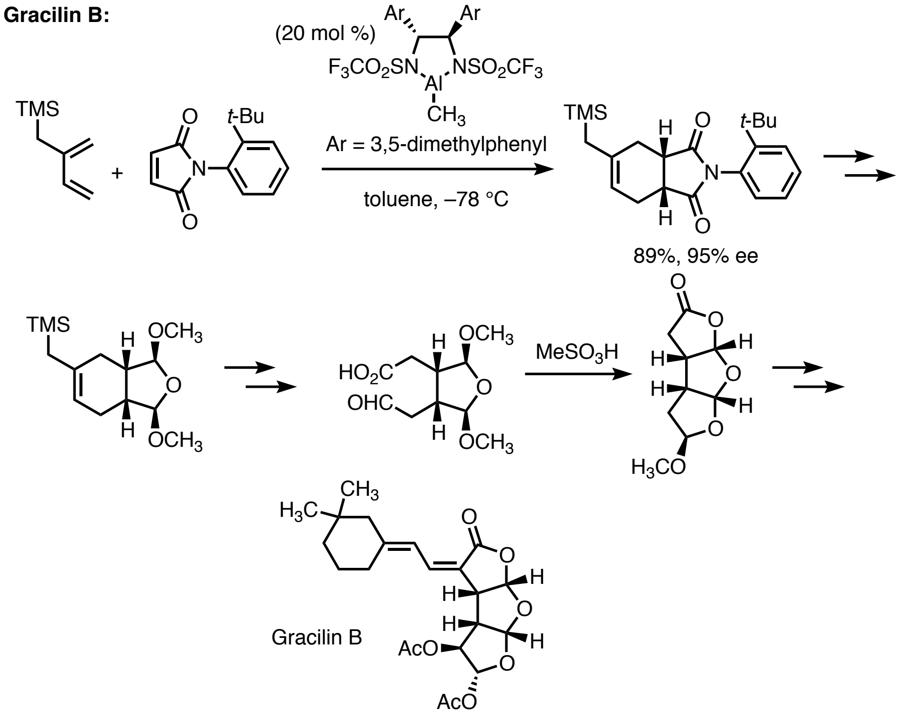
Catalytic, Asymmetric Diels–Alder Reactions – Applications in Synthesis:

Gibberellic Acid:



Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611–3612.

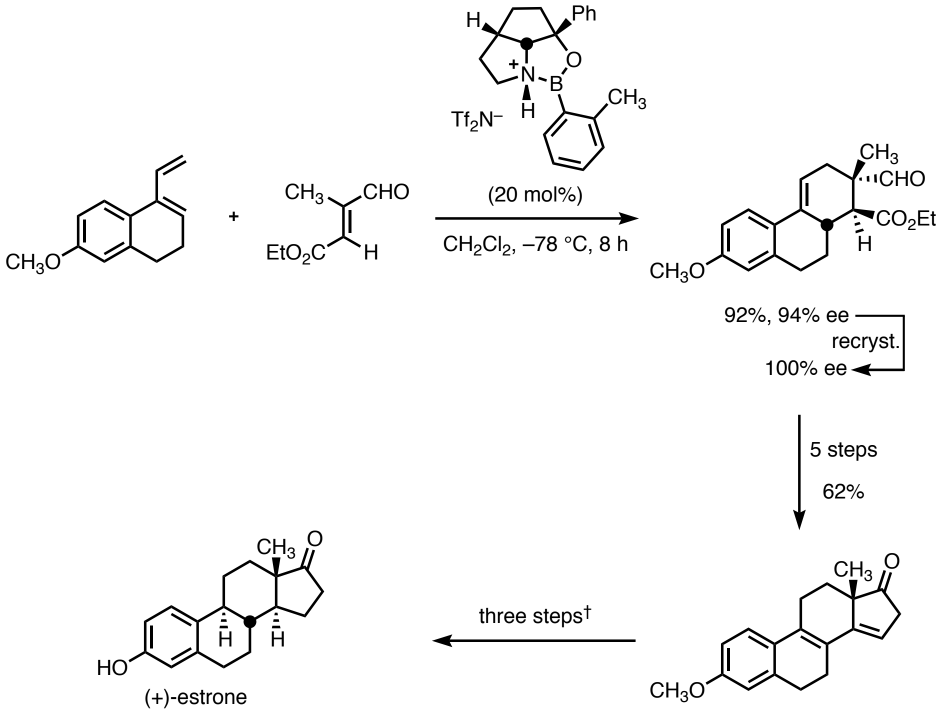
Gracilin B:



Corey, E. J.; Letavic, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 9616–9617.

Kent Barbay

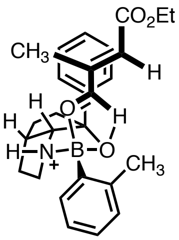
Estrone



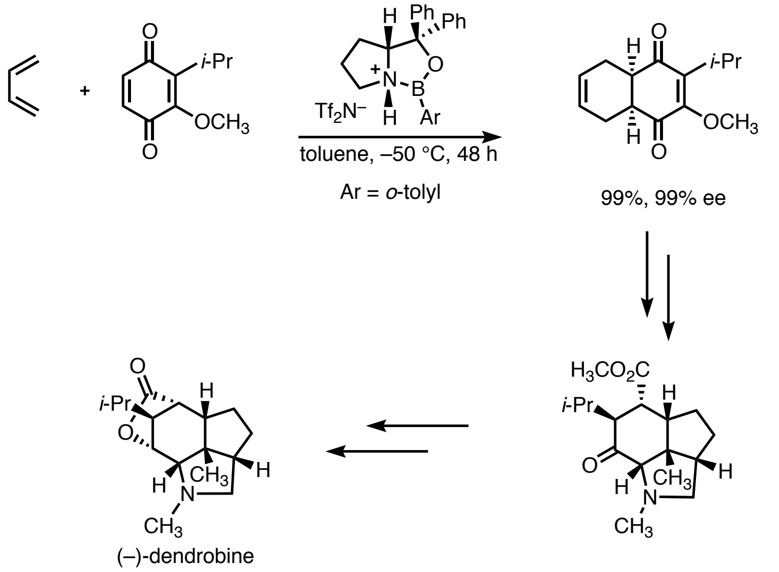
Hu, Q.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004,** *126*, 5984.

† (a). Ananchenko, S. N.; Torgov, I. V. *Tetrahedron Lett.* **1963**, *4*, 1553.
(b) Quinkert, G.; Grosso, M. D.; Dõring, A.; Döring, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmermann, G.; Dürner, G. *Helv. Chim. Acta* **1995**, *78*, 1345.

- Both enantiomers of the catalyst are accessible.
- The following pre-transition-state assembly was suggested:

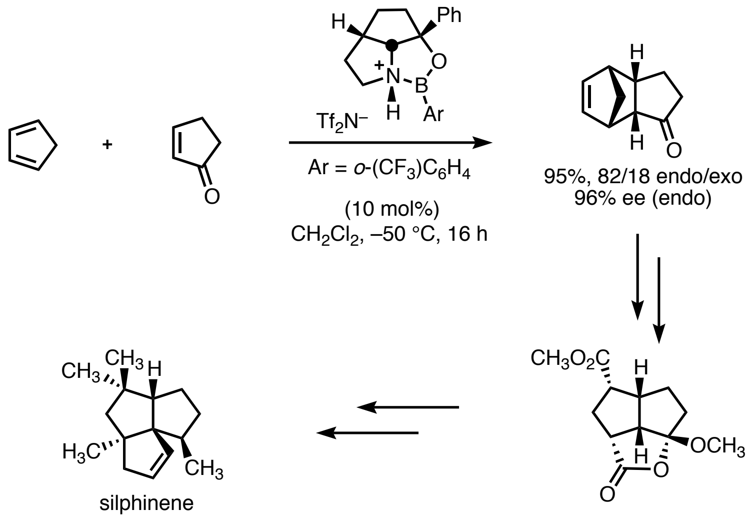


The application of the oxazaborolidinium catalysts to once racemic syntheses has been demonstrated:



racemic synthesis: Kende, A. S.; Bentley, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 4332.

Hu, Q.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 13708.



racemic synthesis: Tsunoda, T.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1983**, *24*, 83.

Hu, Q.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 13708.

Seth B. Herzon